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MUSERLIAN AND LUCAS AND MERCANTI, LLP  
475 PARK AVENUE SOUTH  
NEW YORK, NY 10016

EXAMINER

DIBRINO, MARIANNE NMN

ART UNIT	PAPER NUMBER
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1644

DATE MAILED: 08/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/673,166

Applicant(s)

LEGAL ET AL

Examiner

DiBrino Marianne

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 4/30/04, 1/6/04, 4/4/01, 5/29/01, 3/14/02, 8/20/02 and 8/27/03
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 23-43 is/are pending in the application.
- 4a) Of the above claim(s) 27-29, 31-33, 39, 41 and 42 is/are withdrawn from consideration.
- 5) ☒ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 23-26, 30, 34-38, 40 and 43 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date 10/25/00.
- 4) ☒ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. attached hereto.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

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### DETAILED ACTION

1. Applicant's replies filed 4/30/04 and 1/6/04 to the Action mailed 4/21/04 are nonresponsive because Applicant failed to elect a species of CTL epitope required at item #5 in the Restriction Requirement mailed 11/7/03. However, in view of the content of the Interview Summary of 7/28/04 (attached hereto), the said reply filed 4/30/04 and the reply filed 1/6/04 are acknowledged and have been entered.

In addition, Applicant's amendments filed 4/4/01, 5/29/01, 3/14/02, 8/20/02 and 8/27/03 are acknowledged and have been entered.

2. Applicant's election with traverse of Group I (claims 23-40 and 43), and species of dipalmitoyl lysyl as the lipid moiety, TT 830-843 as the T cell epitope and the spacer RGR in Applicant's reply filed 1/6/04 is acknowledged and has been entered.

Applicant failed to elect a species of CTL epitope required at item #5 in the Restriction Requirement mailed 11/7/03. In Applicant's reply filed 4/30/04, Applicant indicated that "Applicants elected the HIV NEF 68-82 as the CTL epitope. Such a lipopeptide is named TT-NEF at the bottom of Table 8 of the specification and has the following amino acid sequence FPVTPQBPLRMTYK." However, the lipopeptide named TT-NEF at the bottom of Table 8 in the specification is not a CTL epitope per se and has a length of 35 amino acid residues, while the amino acid sequence FPVTPQBPLRMTYK has a length of 15 amino acid residues and contains a "B" which is not a code letter for any amino acid residue.

In response to the Examiner's request, Applicant indicated in a telephone message of 7/28/04 with regard to the said CTL epitope species election, that the elected lipopeptide is SEQ ID NO: 276 amino acid residues 1-43, which is still non-responsive. The Examiner left an additional message. No reply has been received. In addition, the lipopeptide TT-NEF at the bottom of Table 8 of the specification has a one additional amino acid residue at the N terminus, i.e., K, that is not present in SEQ ID NO: 276 which begins with G. In addition, the TT-NEF lipopeptide in Table 8 of the specification has two spacers, one is a non-elected species "GR" following the Palm-K, and the other is the elected species "RGR" that separates the TT 830-843 auxiliary T cell epitope from the CTL epitope amino acid residues 20-34 of SEQ ID NO: 276.

However, in the interest of facilitating prosecution, the Examiner has made the assumption that amino acid residues 20-34 of SEQ ID NO: 276 is the CTL epitope, i.e., FPVTPQVPLRPMYK, the "V" being the correct amino acid residue in place of "B" which is not a code letter for any amino acid residue, and the elected species of lipopeptide is a dipalmitoyl lysyl version of the palmitoyl lysyl peptide TT-NEF shown in Table 8 of the specification.

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The basis for the traversal is that allegedly the claims have the same or corresponding special technical features to distinguish over the prior art since the epitope PADRE linked to a CTL epitope and lipid is not taught by the prior art. Applicant's argument in Applicant's response filed 1/6/04 has been fully considered but is not persuasive.

It is the Examiner's position that the inventions listed as Groups I and II do relate to a single general inventive concept because US Patent No. 5,662,907 discloses two molecules of palmitic acid linked through a Lys containing amino acid linker to a multivalent T helper/auxiliary epitope QYIKANSKFIGITE from tetanus toxin and further linked to a melanoma CTL peptide epitope either directly or using a spacer (especially columns 7 and 8), as enunciated at item #3 of the Restriction Requirement mailed 11/7/03. In addition, base claim 23 is indefinite in the recitation of "wherein the epitopes and the lipid moiety are independently separated from the epitopes by amino acid sequences" as enunciated at item # 10b below, and the claim as broadly interpreted reads on a sequence comprising a T auxiliary epitope, linked to a CTL epitope via spacer molecules and further linked to two palmitic acid residues via a Lys containing spacer. In addition, the 103(a) rejections of record below also apply to instant claim 23.

**The requirement is still deemed proper and is therefore made FINAL.**

Accordingly, claims 27-29, 31-33 and 39 (non-elected species of Group I) and claims 41-42 (non-elected groups II) are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 23-26, 30, 34-38, 40 and 43 read on the elected species.

Claims 23-26, 30, 34-38, 40 and 43 are currently being examined.

3. Applicant is required under 37 C.F.R. 1.821(d) to amend the specification to list the appropriate SEQ ID NOS for sequences disclosed in the specification (for example, in the brief description of the drawings for Fig. 5, i.e., figure 5 discloses two peptide sequences).

4. The disclosure is objected to because of the following informalities:

a. The brief description of the drawings for Fig. 6 should be Fig. 6 A-C.

b. The use of the trademarks VYDAC (page 11 at line 18), ZORBAX (page 11 at line 18) and ELISPOT (the Examiner noted one occurrence of lower case letters, please search for and correct) have been noted in this application. It should be capitalized or accompanied by the <sup>TM</sup> or ® symbol wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner

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which might adversely affect their validity as trademarks. Each letter of the trademark must be capitalized. See MPEP 608.1(V) and Appendix 1.

Appropriate corrections are required.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 23-26, 30, 34-38, 40 and 43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The amendatory material not disclosed by the specification and claims as originally filed is as follows: the recitation in base claim 23 of "neutral membrane" at line 5. The disclosure on page 2 at lines 22-28 and at lines 33-35 and in originally filed claim 1 is of a "neutral medium".

7. Claims 23-26, 30, 36-38, 40 and 43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the . . . claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the claimed lipopeptide and vaccine thereof, recited in the instant claims.

The instant claims encompass a lipopeptide comprising at least one "lipid moiety" and a vaccine comprising said lipopeptide. There is insufficient disclosure in the specification on such a lipopeptide and vaccine comprising said lipopeptide.

The specification discloses that the lipid portion of the lipopeptide can comprise one or several optionally branched or [u]nsaturated chains derived from C10-C20 fatty acids or a steroid derivative, and that it may also be made of or comprise a moiety of palmitic, oleic, linoleic,

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linolenic, 2-aminohexadecanoic acids, pimelutide or trimexautide (especially page 5 at lines 19-32).

The specification does not disclose any lipopeptide used prophylactically as a vaccine.

The instant disclosure does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera, including any lipid or portion thereof. Since the disclosure fails to provide sufficient relevant identifying characteristics, and because the genus is highly variant, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.

8. Claims 23-26, 30, 36-38, 40 and 43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not disclose how to make and use the instant invention, a lipopeptide and vaccine thereof, comprising at least one "lipid moiety" and wherein the vaccine is used for prophylaxis. The specification has not enabled the breadth of the claimed invention because the claims encompass lipopeptides comprising any lipid or portion thereof, and use prophylactically as a vaccine. The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed compositions can be made and used for prophylactically. The specification discloses no working examples with regards to the use of the instant invention for prevention of disease in vivo.

The specification discloses that the lipid portion of the lipopeptide can comprise one or several optionally branched or [u]nsaturated chains derived from C10-C20 fatty acids or a steroid derivative, and that it may also be made of or comprise a moiety of palmitic, oleic, linoleic, linolenic, 2-aminohexadecanoic acids, pimelutide or trimexautide (especially page 5 at lines 19-32).

The specification does not disclose any lipopeptide used prophylactically as a vaccine.

Evidentiary reference the Merck Manual teaches that a vaccine is a suspension of whole or fractionated bacteria or viruses that have been rendered nonpathogenic and is given to induce an immune response and prevent subsequent disease. Evidentiary reference Encyclopedia Britannica Online defines vaccine as a suspension of weakened, killed, or fragmented microorganisms or toxins or of antibodies or lymphocytes that is administered primarily to prevent disease.

There is insufficient guidance in the specification as to how to make and/or use instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

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9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 23-26, 30, 34-38, 40 and 43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Base claim 23 is indefinite in the recitation of "amino acid sequences (spacers)" because it is not clear what is meant.

b. Base claim 23 is indefinite in the recitation of "wherein the epitopes and the lipid moiety are independently separated from the epitopes by amino acid sequences" because it is not clear what is meant.

c. Claim 34 is indefinite in the recitation of "to NH<sub>2</sub> group" because it is not clear what is meant. It is suggested that Applicant amend said claim to recite "to the NH<sub>2</sub> group".

d. Claim 40 is indefinite in the recitation of "p-53" because it is not clear what is meant. It is suggested that Applicant amend said claim to recite "p53".

10.

e. Claim 38 is indefinite in the recitation of "titanic" in line 2 because it is not clear what is meant. It is suggested that Applicant amend said claim to recite "tetanus".

f. Base claim 23 is indefinite in the recitation of "separated from the epitopes by amino acid sequences (spacers) comprising linkages of charged amino acids in a neutral membrane" because it is not clear what is meant.

g. Claim 25 recites the limitation "wherein at least one of the spacers is at least one member of the group consisting of 1 to 10 glycines and arginines" in lines 1-3. There is insufficient antecedent basis for this limitation in the claim. The "spacers" recited in base claim 23 comprise linkages of charged amino acid residues and glycine is not a charged amino acid residue.

11. For the purpose of prior art rejections, the filing date of the instant claims is deemed to be the filing date of the 371 application, i.e., 4/6/99, as an English language translation of the foreign priority document FR 98 04323 filed 4/7/98 has not been provided.

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12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 23, 24, 30, 34-37, 40 and 43 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent No. 5,662,907 (previously provided).

During patent examination, the pending claims must be "given the broadest reasonable interpretation consistent with the specification." Applicant always has the opportunity to amend the claims during prosecution and broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than is justified. In re Prater, 162 USPQ 541, 550 + 51 (CCPA 1969).

US Patent No. 5,662,907 discloses two molecules of palmitic acid linked through a Lys containing amino acid linker to a multivalent T helper/auxiliary epitope QYIKANSKFIGITE from tetanus toxin and further linked to a melanoma CTL peptide epitope either directly or using a spacer (especially columns 7 and 8). US Patent No. 5,662,907 also discloses vaccines comprising the lipopeptides (especially column 2 at lines 15-25).

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).



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15. Claims 23-25, 30, 34-37, 40 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vitiello et al (J. Clin. Invest. 95, 1995, 341-349, IDS reference) in view of US Patent No. 5,935,824 and US 2003/0162719A1.

Vitiello et al teach that most CTL peptide epitopes are poor immunogens so modification by attaching a T helper peptide (HTL) epitope such as tetanus toxoid peptide 830-843 and two lipid molecules such as palmitic acid improves immunogenicity and results in long-term memory CTL induction (especially abstract and Figure 1). Vitiello et al teach that the structure of the lipopeptide is 2 molecules of palmitic acid coupled via a KSS linker, i.e., comprising a linkage of a charged amino acid residue, to the tetanus toxoid 830-843 T promiscuous, i.e, multivalent, auxiliary epitope linked via a AAA linker to HBV core 18-27 CTL peptide epitope (especially Figure 1). Vitiello et al teach that lipid modification of antigenic peptides enhances their immunogenicity (especially paragraph spanning columns 1 and 2 on page 347). Vitiello et al teach that lipid modification of peptides may help them translocate across the plasma membrane into the cytoplasm, leads to the persistence of peptides at the site of injection or in the draining lymph node for sufficient time to induce a CTL response (ibid). Vitiello et al teach that the CTL epitope must be cleaved from the remainder of the lipopeptide in order for it to associate with MHC class I molecules, and that the lipopeptide is 1000-fold less efficient in sensitizing targets for lysis by CTL than the CTL peptide epitope alone in vitro (ibid and continuing onto page 348). Vitiello et further teach that antigenic peptides that bind to class I can be derived from infectious agents such as a peptide from HIV or from cancer cells, (paragraph 2 of column 1 on page 341 and reference 18 on page 349). Vitiello et al teach therapeutic vaccines comprising CTL epitopes from HBV (especially Abstract).

Vitiello et al do not teach that the linker separating the T helper epitope and the CTL epitope comprises charged amino acid residues.

US Patent No. 5,935,824 discloses fusion proteins comprising a domain comprising a hydrophilic spacer comprising either Lys or Arg (especially column 6 at lines 57-58 and the sentence spanning columns 6 and 7). US Patent No. 5,935,824 further discloses that the hydrophilic and basic nature of Arg and Lys residues causes them to be orientated within exposed regions of the fusion protein and increases the likelihood that that linker will be accessible to digestion with endoproteases (especially column 11 at lines 23-27).

US 2003/0162719A1 discloses that peptides such as class I MHC antigens and class II MHC antigens are particularly intractable to transmembrane transport, and that polymers of highly basics subunits such as Arg attached to the peptide can facilitate transport across the cell membrane of an antigen presenting cell (APC) in order to promote or elicit an immune response, and further discloses a poly-L arginine linker of formula CAAA(R)<sub>7</sub>, the "C" being useful when the product is coupled via crosslinking rather than than made by recombinant means (especially column 1 at [0004], [0009], [0013], [0019][0051], [0087], [0144], [0216]).

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US 2003/0162719A1 discloses that the peptides linked to the basic transporting polymers can be produced by using a synthesizer or by recombinant methods (especially [0145]).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have added a hydrophilic spacer comprising either Lys or Arg disclosed by US Patent No. 5,935,824 and by US 2003/0162719A1 (including the species of CAAA(R)<sub>7</sub> minus the Cys residue) between the HTL and the CTL epitope and in between the HTL and the lipid in the lipopeptide taught by Vitiello.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to improve the efficiency of the lipopeptide taught by Vitiello et al since Vitiello et al teach that the efficiency of the lipopeptide comprising the CTL epitope is 100-fold less than the CTL epitope peptide alone and that the CTL epitope must be cleaved in order for it to associate with the MHC class I molecule, and US Patent No. 5,935,824 discloses using hydrophilic spacers comprising Lys or Arg to increase the likelihood that the linker will be accessible to digestion with endoproteases, i.e., will be cleaved, and US 2003/0162719A1 discloses that the transport of peptides such as class I and class II MCH antigens, i.e., CTL and HTL epitopes, respectively, across APC cell membranes is enhanced by attachment to polymers of basic subunits such as Arg. One of ordinary skill in the art at the time the invention was made would have been motivated to do this since the peptide taught by Vitiello et al has a AAA linker between the HTL and CTL epitopes and a linker disclosed by US 2003/0162719A1 is CAAA(R)<sub>7</sub>. In addition, One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to increase the solubility of the lipopeptide in solution. Claim 37 is included in this rejection because the tetanus toxoid 830-843 HTL epitope is a multivalent auxiliary T cell epitope. Claim 43 is also included in this rejection also because vaccine merely comprises a known composition, and as such the term carries little weight absent evidence of structural difference.

16. Claims 23, 24, 30, 35-36, 40 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wiesmuller et al (Int. J. Peptide Protein Res. 40, 1992, 255-260) in view of Lasarte et al (Cell. Immunol. 141, 211-218, 1992).

Wiesmuller et al teach lipopeptides with adjuvant activity that comprise a hydrophilic linker, such as Pam3Cys-Ser(Lys)<sub>4</sub> (especially table 1) and further comprising an antigenic peptide EGFR 516-529, or antigenic HIV gp peptides or antigenic Influenza NP peptides (especially paragraph 2 of column 2 on page 257 and entire article). Wiesmuller et al teach that the lipopeptides are adjuvants, can be taken up by APC and deliver rapidly the B-cell and T helper antigens to the natural processing pathway and presentation in context with MHC class II molecules, no attachment to a carrier protein is necessary, are not toxic, are biodegradable and are more stable than conventional protein vaccines (paragraph spanning pages 257 and 258). Wiesmuller et al teach that MHC class I bound CTL epitope peptides such as NP 147-158 and NP 365-380 linked to a lipopeptide adjuvant induced virus specific CTL by in vivo priming of

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mice. Wiesmuller et al teach use of lipopeptides for in vivo treatment of infection and for vaccine development (especially pages 255-256 at column 1).

Wiesmuller et al do not teach the lipopeptides comprise both an HTL and a CTL epitope and that these two epitopes are separated by a hydrophilic linker.

Lasarte et al teach peptide constructs such as HTL-KK-CTL, i.e., T helper epitope linked to two Lys residues linked to a CTL epitope, including to an HIV gp120 peptide epitope, and that induction of CTL requires help from a HTL epitope and that the KK provides potential proteolytic cleavage sites. Lasarte et al teach that this peptide was only able to induce CTL activity when internalized into splenic cells, i.e., APC, and the APC were injected in vivo (especially abstract). Lasarte et al further teach that a lipopeptide consisting of PAM3-S-glycerlcysteinyul-seryl-serine and a CTL epitope peptide was used to immunize mice, and that the lipophilic moiety was essential for an efficient in vivo priming of CTL (especially paragraph spanning pages 1 and 2). Lasarte et al teach the importance of both internalization and T cell help in vivo induction of CTL, and the extension of constructs such as these to utilize HTL and CTL epitopes from viral antigens to protect against infection and to treat chronically infected individuals (especially page 217 at the last two paragraphs).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the Pam3Cys-Ser(Lys)4 lipid moiety taught by Wiesmuller et al with the HTL-KK-CTL peptide taught by Lasarte et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to more easily internalize the peptide construct of Lasarte et al since Wiesmuller et al teach the importance of the superior properties of using the lipid moiety of lipopeptides as adjuvants, and including to facilitate uptake by APC, and Lasarte et al teach the need for both internalization and T cell help in the efficient in vivo priming of CTL. Claim 43 is also included in this rejection also because vaccine merely comprises a known composition, and as such the term carries little weight absent evidence of structural difference.

17. Claim 37 is are rejected under 35 U.S.C. 103(a) as being unpatentable over Wiesmuller et al (Int. J. Peptide Protein Res. 40, 1992, 255-260) in view of Lasarte et al (Cell. Immunol. 141, 211-218, 1992) as applied to claims 23, 24, 30, 35-36, 40 and 43 above, and further in view of Oseroff et al (Vaccine 16(8), 7/1/98, 823-833).

Wiesmuller et al and Lasarte et al, hereafter the "combined references", have been discussed supra.

The combined references do not teach wherein the HTL epitope is a multivalent auxiliary T cell epitope.

Oseroff et al teach the PADRE epitope is an HTL epitope that is multivalent both in humans and in mice, including in the IA<sup>b</sup> haplotype, including in HLA-A2.1/K<sup>b</sup> mice.

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It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the PADRE epitope taught by Oseroff et al as the HTL epitope in the combination taught by Wiesmuller et al and Lasarte et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to utilize an HTL epitope capable of binding to the MHC molecules of HLA-A2.1/K<sup>b</sup> mice taught by Oseroff et al.

18. Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wiesmuller et al (Int. J. Peptide Protein Res. 40, 1992, 255-260) in view of Lasarte et al (Cell. Immunol. 141, 211-218, 1992) as applied to claims 23, 24, 30, 35-36, 40 and 43 above, and further in view of US Patent No. 5,935,824 and Alberts et al (Molec. Biol. Cell, 2<sup>nd</sup> edition, 1989, page 54).

Wiesmuller et al and Lasarte et al, hereafter the "combined references", have been discussed supra.

The combined references do not teach wherein the spacer is comprised of arginine residues.

US Patent No. 5,935,824 discloses fusion proteins comprising a domain comprising a hydrophilic spacer comprising either Lys or Arg (especially column 6 at lines 57-58 and the sentence spanning columns 6 and 7). US Patent No. 5,935,824 further discloses that the hydrophilic and basic nature of Arg and Lys residues causes them to be orientated within exposed regions of the fusion protein and increases the likelihood that that linker will be accessible to digestion with endoproteases (especially column 11 at lines 23-27).

Alberts et al teach that the C=NH<sub>2</sub><sup>+</sup> group of arginine is very basic because its positive charge is stabilized by resonance.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used a spacer comprising arginine in place of the lysine in the combination taught by Wiesmuller et al and Lasarte et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to prepare a lipopeptide taught by the combined references comprising a linker with potential cleavage sites provided by the very basic amino acid residue Arg disclosed by Albert et al and US Patent No. 5,935,824.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to provide a lipopeptide with increased hydrophilicity as taught by Alberts et al and because US Patent No. 5,935,824 teaches that Lys and Arg are interchangeable as hydrophilic spacer molecules and the combined references teach a positively charged linker is optimal between the HTL and CTL epitopes.

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19. Claims 23, 24, 30, 35, 37, 40 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bessler et al (Res. Immunol. 1992, 143/5, 548-553) in view of GB 2271995A (IDS reference) and US Patent No. 5,750,395.

Bessler et al teach lipopeptides comprising a lipid, such as 3 molecules of palmitic acid, a linker, such as one consisting of S(K)<sub>4</sub>, i.e., positively charge amino acid residues, linked to a T helper epitope, such as the sperm whale myoglobin epitope on page 551 at column 2 that has a net positive charge, and a CTL epitope, such as from HIV proteins. Bessler et al teaches the advantages of using lipopeptides includes water solubility, higher biological activity at lower concentration, and increased stability during storage and non-toxicity (especially discussion). Bessler et al teach that the lipid moiety can replace a carrier molecule and adjuvant when inducing an immune response against low molecular weight antigens and antigens with poor immunogenicity such as oligopeptide antigens from infectious agents (especially column 2 on page 549). Bessler et al teach lipopeptides can be used to improve the efficacy of vaccines or to construct novel synthetic vaccines such as the VP-1 vaccine used prophylactically or S. typhimurium S-form vaccine (especially the paragraph spanning columns 1 and 2 on page 550), or for use in treatment of infections.

Bessler et al do not teach wherein the HTL and CTL epitopes are separated by a linker comprising charged amino acid residues.

GB 2271995A teaches an HIV peptide epitope comprising the sequence GPGR linked via an anionic spacer of between 1 and 5 amino acid residues, plus or minus a neutral spacer, to Lysine and further linked to a protein carrier (entire document, including claims). GB 2271995A teaches that peptide epitopes must be conjugated to an immune enhancer (especially page 1), and that a peptide preparation in order to be injectable must be soluble (especially page 2), and that conjugate vaccines with poor solubility may produce poor immune response (especially page 3 at lines 4-11). GB 2271995A teaches that positively charged amino acid residues and hydrophobic amino acid residues can affect the solubility of the peptide (ibid and page 14 at lines 15-19). GB 2271995A teaches that incorporation of an anionic spacer offsets positive charge in the peptide epitope, rendering the conjugate soluble (ibid).

US Patent No. 5,750,395 discloses use of auxiliary HTL epitopes linked to CTL epitopes via spacer amino acid linkers and further linked to palmitic acid or lipid moieties (especially columns 6-8).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the anionic spacer of GB 2271995A to separate the HTL and CTL epitopes in the lipopeptide taught by Bessler et al as for the lipopeptides disclosed by US Patent No. 5,750,395 .

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One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a soluble and efficient peptide immunogen as taught by GB 2271995A and by US Patent No. 5,750,395, particularly in the instances where the sperm whale myoglobin epitope with a net positive charge and the positively charged linker between the lipid and the HTL epitope both taught by Bessler et al, were used. Claim 43 is also included in this rejection also because vaccine merely comprises a known composition, and as such the term carries little weight absent evidence of structural difference.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to elicit effective CTL responses as disclosed/taught by US Patent No. 5,750,395 and Bessler et al using a soluble peptide construct as taught by GB 2271995A.

20. No claim is allowed.

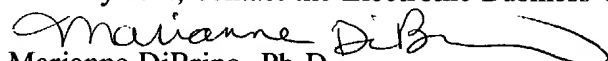
21. The reference crossed out in Applicant's IDS filed 10/25/00 has not been considered because a translation has not been provided. In addition, the two "XP" references listed in said IDS under "Other Documents" have been crossed out and the corresponding correct citations have been written in by the Examiner.

22. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware of in the specification.

23. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Wednesday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Chan Y Christina, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.


Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

  
Marianne DiBrino, Ph.D.

Patent Examiner /Group 1640

Technology Center 1600

August 20, 2004

  
CHRISTINA CHAN  
SUPERVISORY PATENT EXAMINER  
TECHNOLOGY CENTER 1600